DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (mailed on 09/23/2009), Applicants filed a response and amendment received on 01/21/2010. Claim 14 is cancelled; Claims 3-5, 10, 11, 13 and 15 are amended; and Claims 16-17 are new.

Claims 1-13 and 15-17 are pending and will be examined herein.

Withdrawn-Objections to the Specification

2. The previous objection of specification is withdrawn by virtue of applicants' argument.

Withdrawn-Claim Objections

3. The previous objection of Claim 14 for reciting "wherein the volume applied is from about 2-3500 l/min", which should be ---2-3500 l--- since the volume should have unit represented by liter as correctly recited in Claim 15, is withdrawn by virtue of canceling claim 14.

New-Claim Objections

4. Claim 1 is objected to for not reciting a conjunction following step d) of claim 1. In the interest of improving claim form, it is suggested that the "and" be inserted following step d) of claim 1.

5. Claim 1 is objected to in the recitation of "expanded bed adsorption column", "expanded bed column", "chromatographic column" (claim 1, part c)), and "column" (claim 1, part d)), which terms all refer to the same column. In the interest of improving claim form and maintaining consistency, it is suggested that the noted phrases be amended to recite, *e.g.,* "expanded bed adsorption chromatographic column".

Withdrawn-Claim Rejections - 35 USC § 112

6. The previous rejection of Claims 3-5, 10-11, 13 and 15 under 35 U.S.C. 112, second paragraph, for reciting a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) which is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired, is withdrawn by virtue of applicants' amendment in claims 3-5, 10-11, 13 and 15.

7. The previous rejection of Claims 4 and 13 under 35 U.S.C. 112, second paragraph, for the use of phrase "preferably" which renders the claim indefinite, is withdrawn by virtue of applicants' amendment.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-2, 5-13 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lihme et al. (WO 02/096215, published May 12, 2002) as evidenced by Molecular Weight of IgG (last viewed Sep. 11 2009).

The rejection was stated in the previous office action as it applied to previous Claims 1-2 and 5-15. In response to this rejection, applicants have cancelled Claim 14; amended Claims 5, 10, 11, 13 and 15; and added new Claims 16-17; and traverse the rejection as it applies to the newly amended claims. New claims 16-17 are included in the instant rejection for reasons set forth below.

Applicants argue that the Examiner overlooked Lihme's clear teachings (i.e., increasing the temperature which increases flow rate decrease the LF yield in Example 11; thus, it is unclear "what advantage may spring from elevating temperatures during the loading process" (see page 7, Remarks filed on 1/21/2010).

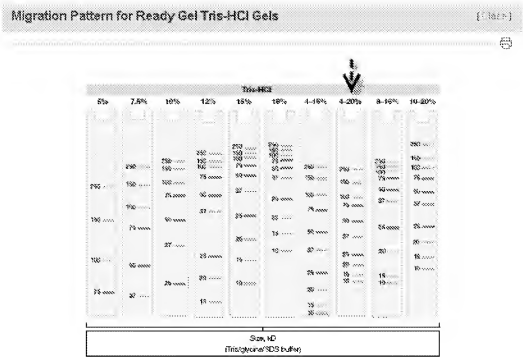
Applicants also argue "nothing in Lihme suggested isolating bio-molecules via a combination of high temperature (at least 40º C) and high flow rate (i.e., at least 1500 cm/hr)"; thus, Lihme's teaching would have lead an artisan away from such combination and notwithstanding the examiner's assertion that Lihme suggested that EBA columns are more efficient and cost effective than other chromatographic techniques (see top of page 8, Remarks filed on 1/21/2010).

Applicants argue that the reference of molecular weight of IgG do not provide the reason to have combined the selected portions of the cited references to produce the claimed invention because it is from unidentified source with an unknown art-effective date (see second paragraph of page 8, Remarks filed on 1/21/2010)

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The prior art publication used here is the publication by the instant inventive entity with additional authors who teach the use of well known Expanded Bed Adsorption (EBA) technology to isolate a biomolecule employing flow rate and temperature encompassed by the instant claims; and the teaching of "more efficient and cost effective" in using an EBA column is not the assertion by an Examiner; but it is an explicit teaching by the published reference by Lihme et al. Applicants alleges that there is no suggestion that EBA columns are more efficient and cost effective by disregarding the overall teachings of Lihme et al. about the EBA technology; which should have been obvious since the publication of Lihme et al. is the publication by one of the instant inventor. As noted in the previous office action, on page 7, bottom, mailed on 9/23/2009, "traditional packed beds work as depth filters that can clog, resulting in increased back-pressure unless the feed is thoroughly clarified. Since no significant pressure builds up in an EBA column, it is possible to apply EBA without the limitations in size and flow rate normally associated with packed-bed columns." It is important to note that, unlike the regular column procedure, the faster flow rate in EBA column unpacks or loosens the EBA resin because the EBA sample runs in opposite direction such as from bottom to top which is the direction of

sample moving against the force of gravity; thus, loosening the packed column adsorbent, particularly useful for an industry requiring a process of very large volume such as dairy industry for milk, for example. Also, the publication by Lihme et al. is an international patent publication (emphasis added) teaching the usefulness of EBA columns for isolating a biological molecule with varieties of parameter for optimization (e.g., temperature vs. flow rate); and it would be unreasonable to anyone if said patent disclosure is to be understood as demoting the use of EBA columns with disclosed various parameters (e.g., increased flow rate which is the benefit of increased temperature) for preparing a biological molecule. Thus, in view of teachings by Lihme et al. reference, as noted previously, the recitation of "more efficient and cost effective" by Lihme et al. is not an assumption but explicit teaching for the use of EBA columns (e.g., cost, time and/or any other factors that is necessary for one skilled in the art). If the overall increase in product yield is needed, it would be obvious for one skilled in the art to adjust the operation appropriately according to the teaching of Lihme et al. who disclose "In each step, the number and size of columns connected in parallel may be adjusted in order to obtain optimal market adaptation" (see page 24, lines 21-25). It is noted that an evidentiary reference do not has to be before the priority date of instant application; and the molecular weight of IgG is well known in the art as attached in the evidentiary reference (disclosing the molecular weight of about 150 kDa meets the instant limitation of "at least 2 kDa" in claim 5). Also, it is well known for one skilled in the art who used the 4-20% gradient gel (the one that used by Lihme et al. as explained below), the 2kDa protein would not even show up in 4-20% gel because they are so

small the 2kDa protein passed through the gel with a loading dye, and it is below the low resolution limit of the 4-20% SDS-PAGE gel. Thus, the size of any protein band shown by Figures 5-8 by Lihme et al. is larger than 2 kDa. Lihme et al. disclose the "The purity of the elutes was determined by SDS Polyacrylamide electrophoresis using precast gels : **SDS Page 4-20 %** Tris-Glycine Gel 1.0 mm cat. no. 345-0033 BioRad, running buffer cat. no. EC2675 Invitrogen and sample buffer cat. no. EC2676, Invitrogen" (emphasis added; see Example 7 on top of page 31). The comparison of the migration pattern of marker shown below provided by Bio-rad company ("Migration Pattern" from http://www.bio-rad.com/prd/en/US/adirect/biorad?cmd=BRCatgProductDetail&productID=239101#) and the migration position of the IgG in the reference of Lihme et al. supports the fact that the IgG is about 150 kDa; and definitely encompassed by the recited limitation of "at least 2 kDa" in instant claim 5.



Standard protein migration on Ready Gel Tris-HCl precast gels. The banding patterns indicate the optimal separation ranges (in kD) for each acrylamide percentage in combinations with the specified buffer system. Migrations are based on the leading dye front being run to the bottom of a gel.

Lihme et al. also teach the EBA column with "particularly at most 100 µm" in particle size (see page 17, line 10); meeting the limitation of newly added claim 16.

The newly added claim 17 recites "the volume applied per litre of adsorbent in one hour is at least 100 l" which encompasses 100 l/hour since the term "per litre of adsorbent" does not limit the size of column resin; thus, the claim has been interpreted as requiring the flow rate of at least 100 l/hour. In view of the teaching by Lihme et al. [i.e., Since no significant pressure builds up in an EBA column, it is possible to apply EBA without the limitations in size and flow rate normally associated with packed- bed columns." (emphasis added, see page 2, lines 13-19)], and also explicit teaching such

as "A 690,000 litre whey stream per day" can be processed by the EBA column (see page 45, line 1; i.e., 28750 l/hour); thus, meeting the limitation of instant claim **17**.

As similarly noted in the previous office action, Lihme et al. teach a method for purifying LP (lactoperoxidase) comprising steps: adjusting a pH of sweet whey (limitation of instant Claim 1a); loading on column C at 50ºC which teach bringing the bio-molecule-containing fluid to a temperature of 50ºC since the sample has to be 50ºC to operate EBA column at that temperature (limitation of Claim 1b); applying the sample into a EBA column, eluting LP in view of LP (i.e., lactoperoxidase, limitation of instant claims **6-7**) eluted data shown in the Table at the bottom of page 36 (limitation of claim 1c, part, and claim 1d-e), see the Example 11. Lihme et al. also recites instant method steps in the Claim 1 on page 49; wherein the Claim 1 of Lihme et al. teach a method of performing an Expanded Bed adsorption column for fractionation of a sample in various conditions. More specifically, according to Claim 1 of Lihme et al., Lihme et al. teach a method for the fractionation of a protein-containing mixture wherein the protein-containing mixture is selected from the group consisting of **milk** (meeting instant claims **8** and **9**), milk derived products, milk derived raw materials, vegetable derived products, vegetable derived extracts, fruit derived products, fruit derived extracts, fish derived products, and fish derived extracts, said method comprising the steps of: a) optionally adjusting the pH of the mixture; b) applying said mixture to an adsorption column comprising an adsorbent, said adsorbent comprises a particle with at least one high density non-porous core, surrounded by a porous material, the adsorbent having a particle density of at least 1.5 g/ml and a mean particle size of at most 150 μm ; c)

optionally washing the column ; d) eluting at least one protein from the adsorbent." Thus, meeting all limitations of instant Claim 1 except the flow rate of at least 1500 cm/hour. The Figure 6 shows that some of whey proteins have molecular weight similar to IgG (which is 150000 Daltons, see Molecular weight of IgG, page 2, top right, which meets the limitation of at least 2 kDa in instant claim **5**).

Lihme et al. does not teach linear flow rate of at least 1500 cm/hour; a loading sample volume of at least 10 liters, 2-3500 l or at least 50 l in the Example 11 as noted above.

However, Lihme et al. teach "In the expanded bed state, the distance between the adsorbent particles result in a free passage of particulate impurities in the feed stream. By contrast, traditional packed beds work as depth filters that can clog, resulting in increased back-pressure unless the feed is thoroughly clarified. Since no significant pressure builds up in an EBA column, it is possible to apply EBA without the limitations in size and flow rate normally associated with packed- bed columns." (emphasis added, see page 2, lines 13-19). Furthermore. Lihme et al. also teach the method above to be performed at flow-rate of about 5-50 cm/min (i.e., about 3000 cm/hour; instant limitation of "at least 1500 cm/hour" in claim **1c and 13**) in view of Claim 2 on page 49. Lihme et al. also teach a method of EBA column chromatography by loading sample of 3180 litre of whey sample onto an EBA column for purifying LP (as shown in Example 18 on page 43, line 24). Lihme et al. teach the adsorbent mean particle size used in EBA column can be 59 µm and density of 3.3 g/ml (see description of Figure 9 on page 9, lines 13-14); meeting the limitations of Claims **10-12**.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify an Expanded Bed adsorption (EBA) column and/or process disclosed by Lihme et al. so that said method applies a higher flow rate (3000 cm/hour, for example), any size of biological sample (e.g., up to more than about 3000 liter) and/or many different size of adsorbent particle size (for example, 59 um particle size with density of 3.3 g/ml as noted above) with a reasonable expectation of success because Lihme et al. teach the sample size and flow rate is not limitations in EBA column system. The motivation to do so is provided by Lihme et al. who teach the usefulness of Expanded Bed Adsorption column is "more efficient and cost effective production method" in a chromatographic separation technique in the field of biotechnology industry (see page 1, lines 30-36). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

9. The previous rejection of Claims 1-13 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lihme et al. (WO 02/096215, published May 12, 2002) as evidenced by Molecular Weight of IgG (last viewed Sep. 11 2009) as applied to claims 1-2, 5-15 above, and **further in view of** Olander et al., (Scandinavian Dairy Information, 2001, no. 2., pp. 22–25) is maintained.

Applicants argue Olander, cited for teaching "an industrial scale EBA column having 265 liters of adsorbent and having a diameter of 1.5 meter" fails to cure the deficiencies of the primary references.

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. In view of reasons above, there is no deficiency by the primary references and the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art. Also, the adjustment of size of column in EBA column is well known for one skilled in the art as exemplified by Olander et al.

As noted previously, the teachings of Lihme et al. as evidenced by "Molecular Weight of IgG" are shown as set forth above.

Lihme et al. as evidenced by "Molecular Weight of IgG" do not teach a EBA column having about 100 to 1000 l of adsorbent (instant Claim 3); and having a diameter of about 50 cm to 200 cm (instant Claim 4).

Olander et al. teach an industrial scale EBA column having 265 liters of adsorbent and having a diameter of 1.5 meter (i.e., 1500 cm), see bottom of left column, page 25.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify an Expanded Bed adsorption (EBA) column and/or process disclosed by Lihme et al. so that said method use a large industrial scale EBA column as disclosed by Olander et al. with a reasonable expectation of success because it is well known for one skilled in the art to make and use appropriate size of column for a volume of sample of interest as shown by Lihme et al. who teach the sample size and flow rate is not limitations in EBA column system. The motivation to increase or adjust the EBA column size so is provided by Lihme et al.

who teach the usefulness of "more efficient and cost effective production method" in a chromatographic separation techniques in the field of biotechnology industry (see page 1, lines 30-36); or Olander et al. who disclose the industry scale (i.e., a large EBA column) EBA technology is "a cost-effective industrial-scale method for production of components from whey and milk" (see top of left column, page 22). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Conclusion

10. Claims 1-13 and 15-17 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered section in this Office action to be fully responsive in prosecution.

Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALEXANDER D. KIM whose telephone number is (571)272-5266. The examiner can normally be reached on 10AM-6:30PM.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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